REMARKS

Claims 29-35 remain in this application, of which 29-32 have been withdrawn from consideration.

I. Rejections Under 35 USC 112, first paragraph:

On page 2 of the November 10, 2005 Office action, the Examiner rejected claims 33-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, i.e. as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In support of the rejection, the Examiner has presented a list of the factors that he has considered in his analysis.

In response, Applicants note that to reject a disclosure for lack of enablement, the Examiner must provide evidence or technical reasoning. Without a reason to doubt the truth of the statements made in the application, the application must be considered enabling (In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993); In re Marzocchi, 439 F.2d 220, 223 (CCPA 1971)). The Examiner begins his description of the state of the prior art and level of skill in the art with the statement "Farnesyl transferase inhibitors (FTIs) have been described as Kelland as a potential treatment for breast cancer, but with limited success for single agent activity." Applicants respectfully disagree with this characterization of Kelland's view of the activity of FTIs in breast cancer. Kelland (Expert Opin. Investig. Drugs (2003) 12(3):413-421) states on line 15 of the first page (page 413) of his article: "In terms of their potential use in the chemotherapeutic treatment of advanced breast cancer, a Phase II trial of R115777 (using either continuous or intermittent twice-daily oral dosing) **has demonstrated promising activity** (~10% partial response rate)." (emphasis added). Furthermore, on page 419 Kelland goes on to say: "However, the FTIs clearly act independently of *ras* gene status and R115777, in particular, does appear to possess activity in advanced breast cancer **as a monotherapy**." (emphasis added). The effects of R115777 are described in more detail on pages 416-417

of the Kelland article. Clearly Kelland, an acknowledged expert in the field from St. Georges Hospital Medical School in London, believes that the FTI R115777 has promising activity as a singe-agent activity. With respect, applicants contend that without providing substantial evidence or technical reasoning to advance a conflicting opinion, it is inappropriate for an Examiner to characterize the state of the art as "limited success for single agent activity" when the Examiner is in possession of the writings of an acknowledged expert in the field and views expressed therein do not support the Examiner's views.

The Examiner on page 3, section (b) of the November 10, 2005 Office action, has focused additional comments on suggesting that FTIs will unlikely be used for monotherapy and that their best use may be in combination therapy. In response, applicants do not dispute the fact that combination therapy may be an attractive option for use of FTIs, and this of course is encompassed in Claim 33 (which uses "comprises" to allow for the possibility of other agents or procedures being part of a treatment), but do respectfully disagree with the Examiner's characterization of the Head et al. article (Expert Opin. Investig. Drugs (2003) 8(1):163-178) in his use of the quote: "……it would appear that FTIs are unlikely to be used as monotherapy for advanced disease." Applicants respectfully contend that an examination of the full context of this statement would not lead one to believe that FTIs will not have any use as single agents. Thus a more complete quote from that section on page 174 of the article reads as the following:

"From the low objective response rates seen in Phase II clinical trials to date, it would appear that FTIs are unlikely to be used as monotherapy for advanced disease. **However, a significant number of stabilisations have been seen** and, given the potential cytostatic effects of FTIs, this aspect should be included in future trials assessing clinical efficacy. **For some tumours, FTIs could be used as maintenance therapy after tumour cytoreduction**. However, a more promising effect appears to be the added response that may occur when FTIs are given in combination with conventional therapies, such as chemotherapy, hormonal treatment or other signal transduction inhibitors." (emphasis added).

Thus this author, in addition to the potential use of FTIs in combination therapy, clearly sees a potential use of FTIs for tumor stabilization and maintenance therapy. Furthermore, Kelland (Expert Opin. Investig. Drugs (2003) 12(3):413-421) reports in Table 1 promising partial response results for breast cancer, complete responses in myeloproliferative disorders, partial responses for gliomas, a 29% response rate for leukemias, and 14% stable disease for non-small cell lung cancer. In addition, on page 417 Kelland reports single-agent activity in patients with relapsed and refractory acute myelogenous leukemia (AML) and CML, including five complete responses in AML and seven responses in CML where reductions in bone marrow leukemia blasts was to <5%. In summary, clearly both of the Expert Opinion articles cited by the Examiner demonstrate that FTIs have shown promising results in monotherapy treatment of a variety of hyperproliferative disorders, ras-mediated or not. In addition, applicants would like to point out that the FTI compounds of the instant invention have demonstrated prolonged stabilization of disease in a clinical trial including patients with a variety of tumors, including colorectal, bronchoalveolar, renal cell, hepatocellular, and thyroid carcinoma (see Moulder, S.L. et al. (2004) Clin. Cancer Res. 10:7127-7135 (**attached**)) Applicants concede that FTIs may not be suitable for every patient or every type of hyperproliferative disorder, but that is typically the case for all therapeutics that have been discovered to date, particularly in the area of oncology. However, the fact that some hyperproliferative disorders may exist that are not effectively treated by the compounds of the instant invention does not necessarily render claims such as claim 33 or 35 unpatentable (e.g. see MPEP **2164.08(b)** Inoperative Subject Matter). One of ordinary skill in the art in pharmacology would readily be able to determine without undue experimentation if there were any embodiments of the methods of the instant invention that were inoperable.

Applicants also note that Claims 33-35 do not require that the method of treatment increases patient survival or reduces tumor size. The term "treating" is defined in the instant specification, except where indicated otherwise, as "reversing, **alleviating, inhibiting the progress of,** or preventing the disorder or condition to which such term

applies, or one or more symptoms of such disorder or condition." (emphasis added). Stabilization of disease, maintenance therapy, or other treatments that alleviate symptoms of the disease (e.g. physical and psychological effects resulting from the increase in size of tumors; pain), and thus potentially enhance a patient's quality of life, are well recognized in the art as medically useful treatments, even if life is not extended. To exemplify the importance attributed to quality of life of cancer patients by the medical community applicants have attached an article from the American Cancer Society's website indicating that this is area of great importance and intensive study for this organization, and also an abstract (from Payne, S.A. (1992) Soc. Sci. Med. 35(12):1505-1509) indicating the importance of quality of life considerations, particularly when a treatment is palliative rather than curative.

The Examiner has indicated that "no data is given for any *in vitro* or *in vivo* studies to give any indication of the pharmacological effectiveness of the instant invention." In response, applicants indicate that the compounds of the instant invention have been demonstrated to be active inhibitors of farnesyl transferase *in vitro* and in ras-transfected cell lines, have *in vivo* anti-tumor activity against 3T3 H-ras tumors in mice, and in a Phase I clinical trial have demonstrated prolonged stabilization of disease in patients with a variety of tumors, including colorectal, bronchoalveolar, renal cell, hepatocellular, and thyroid carcinoma. These studies are described in Moulder, S.L. et al. (2004) Clin. Cancer Res. 10:7127-7135 (**attached**); see for example the Introduction, last three paragraphs, page 7127-7128, table 1 on page 7128, and page 7135, penultimate paragraph, beginning "Although...".

The Examiner alleges that "The high degree of unpredictability is well recognized in the art", and refers to sections of Saha et al (2005) Bioorganic and Medicinal Chemistry letters, article in press, e.g. Table 1. However, applicants respectfully contend that the alleged evidence that the Examiner has presented merely demonstrates an SAR (structure-activity relationship) for the compounds that are the subject of the article. This is readily apparent on reading column 2, page 2 or the article where it states: "Several members of our initial library had activity and a sense of SAR was immediately apparent

as shown in Table 1" Thus, applicants respectfully contend that this table merely demonstrates the author's strategy to increase potency of their initial active compounds, and in no way represents unpredictability of the art. Such SAR techniques are standard procedures in medicinal chemistry in order to refine the characteristics of lead compounds in order to obtain new compounds with the most desirable properties (e.g. high potency, high solubility, high stability etc). In the case of FTIs the final products of such procedures are all typically low or sub- nanomolar potency inhibitors (e.g. see R115777, SCH66336 and BMS-214662, Kelland (Expert Opin. Investig. Drugs (2003) 12(3):413-421), pages 416-418).

In response to the Examiner's comments regarding use of FTI inhibitors either alone, or in combination with other anti-tumor agents, such as those described in Claim 35, applicants respectfully contend that methods of using FTI inhibitors, either alone or with such combinations of anti-cancer agents are routine in the field of oncology, and that one of skill in the art would know either how to combine such agents, or how to carry out routine tests in order to find the best regimen for treatment. Applicants would also like to respectfully remind the Examiner that it is well established law that clinical data is not required for patentability of a method of treatment using a new compound with demonstrated anti-tumor activity in accepted models of disease.

Accordingly, applicants respectfully submit that the methods described in claims 33-35 are fully enabled, that the Examiner has failed to provide sufficient evidence or technical reasoning to demonstrate that the compounds of the instant invention will not work as described in the methods of claims 33-35, and that all rejections under 35 USC 112 first paragraph have been overcome. Applicants thus respectfully request the withdrawal of these rejections.

II. Rejections Under 35 USC 112, second paragraph:

On page 5 of the November 10, 2005 Office action, the Examiner rejected Claim 34 under 35 USC 112, second paragraph, as allegedly being indefinite with respect to the

use of the terms "head" and "neck" cancer, and "gynecological" cancer. In response applicants respectfully point out that these are standard terms with well understood meaning in the field of oncology. These terms are standard terms used in the classification of certain types of cancer. As evidence of this applicants have attached copies of pages from the National Cancer Institute's (NCI) web site where terms commonly used in the oncology field are defined. A section from the NCI website is also included which describes what kind of cancers are considered cancers of the head and neck. Applicants have also attached sections from DeVita et al. (1993) Cancer: Principles and Practice of Oncology (4th Edition), a standard well-respected text in the field of oncology, that has chapters on head and neck and gynecological cancers and describes what kind of cancers are typically grouped under these categories. The NCI and DeVita excerpts make it clear that "head and neck" cancers include tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, oropharynx, larynx and hypopharynx, and salivary glands (see for example pages xxx, xxxi, 574, 631 and 655 of DeVita). It is also apparent that "gynecological" cancers include all female genital tract cancers (e.g. cancers of the vulva, vagina, cervix, endometrium, uterus and fallopian tubes), including cancer of the ovaries (see for example pages xxxvii, 1152 and 1226 of DeVita). Applicants thus maintain that the meaning of claim 34 will be clear to one of skill in the art as the meaning of the terms in the context of oncology are well known in the art.

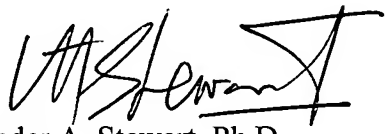
Accordingly, applicants respectfully submit that all rejections under 35 USC 112 second paragraph have been overcome and request their withdrawal.

III. Conclusion

In view of the arguments and amendments set forth above, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection or objection, and that a timely Notice of Allowance be issued in this case.

Agent for Applicants can be reached at the telephone number and address below.

Respectfully submitted,



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Featured Article

A Phase I Open Label Study of the Farnesyltransferase Inhibitor CP-609,754 in Patients with Advanced Malignant Tumors

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ABSTRACT

Purpose: **The purpose of this phase I clinical trial was to determine the maximum-tolerated dose and toxicity of CP-609,754 in patients with solid tumors refractory to standard therapies, to determine the cellular effects of CP-609,754 on its molecular target (farnesyltransferase), and to determine the recommended phase II dose (RP2D) of this agent.**

Experimental Design: **Consenting patients with adequate bone marrow, liver, and renal function were enrolled with an accelerated dose strategy with single-patient parallel cohorts in whom the drug was given orally either once or twice daily. Once a dose-limiting toxicity was encountered or two patients developed Common Toxicity Criteria ≥ grade 2 toxicities, a modified Fibonacci sequence was initiated. Blood samples were collected during cycle 1 for pharmacokinetic and pharmacodynamic analyses.**

Results: **A total of 68 cycles of CP-609,754 was administered to 21 patients enrolled in this study. The dose escalation was from 20 mg once daily to 640 mg twice per day, and at the highest dose level, one of six patients developed a dose-limiting toxicity of grade 3 neuropathy. The drug was otherwise well tolerated, and the maximum-tolerated dose was not reached because of the large number of tablets that would have been required for additional dose escalation. Pharmacokinetic analyses showed a proportional increase in exposure with dose, rapid oral absorption, and a half-life of ~3 hours. Pharmacodynamic results predict a 95% maximal inhibition of peripheral blood mononuclear cell farnesyltransferase activity 2 hours postdose, on average, with a dose of 400 mg twice per day of CP-609,754.**

Conclusions: **On the basis of the safety findings and the pharmacokinetic and pharmacodynamic analyses, the RP2D of CP-609,754 is ≥640 mg twice per day.**

INTRODUCTION

The Ras oncogene has an activating mutation in 30% of all human tumors and plays a key role in transducing extracellular signals involved in cancer cell proliferation and survival (1). Blocking mutated Ras has been shown to reverse malignant transformation in preclinical models (2), additionally supporting the hypothesis that inhibition of Ras can be used as antineoplastic therapy. Ras proteins transduce growth and differentiation signals from receptor tyrosine kinases to the cell nucleus where gene transcription is initiated (3). Protein prenylation (attachment of a thiol-ester) is required for membrane localization and subsequent signal transduction by the Ras oncoprotein (4, 5). The thiol-ester attachment of a farnesyl moiety is catalyzed by farnesyltransferase, an enzyme that can be specifically targeted to inhibit posttranslational processing of proteins such as Ras (6).

Although ras-driven cell proliferation is a valid target for biological therapy, farnesylated proteins other than Ras may also contribute to the mechanism of action of these drugs (7). RhoB is a protein that can undergo farnesylation or geranylgeranylation and is involved with proliferation, adhesion, cytoskeleton organization, and induction of apoptosis (8, 9). Treatment with farnesyl transferase inhibitors increases levels of geranylgeranylated RhoB, which can induce apoptosis (10, 11). Additional research is needed to determine the exact mechanism of action of farnesyl transferase inhibitors; however, because of the largely cytostatic effects of these compounds in preclinical experiments, it is likely that these drugs will require prolonged and continuous exposure to maximize efficacy (12).

CP-609,754 [chemical name: 6-[(4-chlorophenyl) hydroxyl (1-methyl-1-H-imidazol-5-yl) methyl]-4-(3-ethynylphenyl)-1-methyl-2-(1H)-quinolinone, (2R,3R)-2,3-dihydroxybutanediote (1:1)] is a D(-) tartrate salt (Fig. 1) that shows selective inhibition of farnesyltransferase with both *in vitro* and *in vivo* models (Table 1). The IC_{50} for inhibiting farnesylation of recombinant human H-Ras is 0.57 ng/mL and recombinant K-Ras is 46 ng/mL. Kinetic studies with recombinant human farnesyltransferase indicate that CP-609,754 is competitive for the prenyl acceptor (H-Ras protein) and noncompetitive for the prenyl donor farnesyl PP_I, suggesting that the compound interacts with the farnesyltransferase-farnesyl PP_I complex and competes for the binding of the Ras protein. Additional studies indicate that

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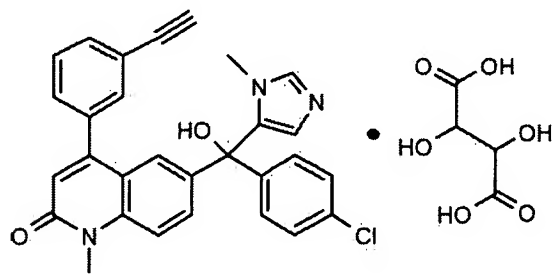

Fig. 1 The chemical structure of CP-609,754.

CP-609,754 is a reversible inhibitor of farnesyltransferase with a slow on/off rate.

CP-609,754 inhibits farnesylation (IC_{50} = 1.72 ng/mL) of mutant H-Ras in 3T3 H-ras (61L)-transfected cell lines with SDS-PAGE analysis of [^{35}S]methionine-labeled material. This effect is not seen in K-Ras transfected cell lines even at concentrations up to 4790 ng/mL. Because K-Ras protein is alternatively prenylated by GGTase-1 in the presence of farnesyltransferase inhibitors, it cannot be separated from farnesylated K-Ras during SDS-PAGE analysis of [^{35}S]methionine-labeled proteins. Similar analysis with tritiated prenyl precursors instead of [^{35}S]methionine confirms that CP-609,754 selectively inhibits farnesylation of both H- and K-Ras proteins in 3T3 transfectants.

CP-609,754 has *in vivo* antitumor activity against 3T3 H-ras (61L) tumors. With twice daily oral dosing of CP-609,754, tumor regression is achieved with a dose of 100 mg/kg; the ED_{50} for tumor growth inhibition is 28 mg/kg. With continuous i.p. infusion of CP-609,754, tumor growth is inhibited by >50%, and tumor farnesyltransferase activity inhibited by >30% in mice in which the plasma concentration of CP-609,754 is maintained above 118 ng/mL. On the basis of these findings, it was projected that CP-609,754 will inhibit farnesyltransferase activity and be clinically efficacious against ras-expressing tumors if plasma concentrations of CP-609,754 are maintained above 118 ng/mL.

PATIENTS AND METHODS

Patient Selection. Twenty-one patients were enrolled onto this phase I trial. The University of South Florida Institutional Review Board approved this trial, and verbal and written informed consent was obtained from all patients. Eligible patients had a diagnosis of an advanced solid tumor that was refractory to standard therapies or for which no standard therapy existed. Enrollment criteria included measurable disease, adequate bone marrow function (absolute neutrophil count ≥ 1500 cells/mm^3, platelets ≥ 100,000 cells/mm^3), bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤ 2.5× the upper limits of normal or ≤ 5× the upper limits of normal with documented liver metastasis, serum creatinine ≤ 1.5× the upper limits of normal or an estimated creatinine clearance ≥ 60 mL/min, Eastern Cooperative Oncology Group performance status of 0 to 2, life expectancy > 12 weeks, and age ≥ 18 years. Exclusion criteria included a history of chemotherapy, radiation therapy, immunotherapy, and/or other investigational agents within 4 weeks of study entry (6 weeks for previous treatments with carboplatin, nitrosoureas, or mitomycin), radiotherapy to >30% of bone marrow containing areas, history of bone marrow transplantation, history of central nervous system malignancy, serious concomitant medical disorders incompatible with evaluating the study drug, clinically significant gastrointestinal abnormalities, including requirement for i.v. alimentation, malabsorption syndromes, and active peptic ulcer disease. Patients with a history of cerebrovascular events, uncontrolled seizure disorder, uncontrolled infection, history of sensitivity to imidazole containing drugs, chronic steroid therapy, significant laboratory abnormalities requiring medical intervention, and pregnant and breastfeeding women were also excluded from study entry.

Drug Supply and Treatment Schema. CP-609,754 was manufactured by Pfizer, Inc., and supplied as 10- or 50-mg tablets administered on an empty stomach (at least 1 hour before or 2 hours after food intake). This was an open-label, dual cohort, phase I dose escalation trial to establish the maximum-tolerated dose, dose-limiting toxicity (DLT) and a recommended phase II dose (RP2D) of CP-609,754. Initially, the drug was administered on a once daily oral dosing schedule with a cycle of therapy defined as a 28-day period of study drug administration; however, a second parallel cohort was added to explore a twice daily dosing schedule after initial pharmacokinetic analysis revealed the drug's half life to be <12 hours. The starting dose for this study was 20 mg/day based on preclinical pharmacology and toxicity data. In cycle 1, day 1 and day 15 doses were administered during a 24-hour hospitalization to monitor for toxicity and to collect blood for pharmacokinetic and pharmacodynamic study end points. All other doses were given on an outpatient basis with weekly monitoring for toxicity. After the first three patients completed 15 days of therapy at a starting dose of 20 mg/day, two new cohorts were initiated with one patient per cohort. The first cohort received the same total daily dose, but CP-609,754 was administered on a twice daily dosing schedule. The second cohort received an escalated dose administered once daily. Dose escalation initially followed an accelerated dose strategy with one subject per cohort and a 100% dose escalation once the lower dose cohort had safely completed 15 days of therapy. A modified Fibonacci dose escalation design was initiated at the dose level in which one subject experienced a DLT or two subjects at the same or different dose level developed Common Toxicity Criteria ≥ grade 2 toxicities. This

Table 1 Inhibitory activity of CP-609,754

Assay	IC_{50} (ng/mL)
Inhibition of recombinant (human) farnesyltransferase activity with H-Ras protein	0.57
Inhibition of recombinant (human) GGTase I activity with CAAX-mutant of H-Ras protein	329
Inhibition of recombinant (human) farnesyltransferase activity with K-Ras protein	46
Inhibition of recombinant (human) GGTase I activity with CAAX-mutant of K-Ras protein	1820
Inhibition of farnesylation of mutant H-Ras in intact 3T3 H-ras (61L) cells	1.72

Abbreviation: GGTase, geranylgeranyl transferase.

design increased all subsequent cohorts to three to six patients with subsequent dose escalations of 67, 50, 40, and 33% of the prior dose level. The maximum-tolerated dose was defined as the dose of CP-609,574 that produced DLT in <33% of subjects treated at a given dose level. At the maximum-tolerated dose, each of the two dosing regimens, once daily and twice per day, was to be evaluated by expanding the cohort to six subjects.

DLT was defined by adverse events according to the National Cancer Institute, Common Toxicity Criteria (version 2.0) and included grade 4 neutropenia persisting for >7 consecutive days or associated with fever > 38°C; grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding requiring platelet transfusion; grade 4 nonhematologic toxicity related to the study drug; grade 3 nonhematologic toxicity that failed to resolve to <grade 2 within 7 days (except nausea, vomiting, fatigue, or asthenia); or nausea and/or vomiting (>grade 2) that persisted with maximum treatment and/or prophylaxis.

Chemistry and hematologic measurements were completed weekly while patients were receiving therapy with additional clinic visits scheduled at the discretion of the investigator. In the absence of disease progression or unacceptable toxicity, treatment was to continue for a maximum of 12 cycles (48 weeks), with provisions for additional treatment in responding patients.

Response Evaluation. Tumor measurements were repeated every two cycles. Standard Response Evaluation Criteria in Solid Tumors were used to evaluate response. The best overall response was recorded from the start of treatment until disease progression or recurrence.

Pharmacokinetics. Blood specimens for CP-609,754 analysis were collected in sodium heparinized tubes on days 1 and 15 of cycle 1. For once daily dosing, the sampling schedule was predose and 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing. For twice daily dosing, the sampling schedule was predose and 1, 2, 3, 4, 6, 8, and 12 hours after each dose. Specimens were centrifuged at ~1500 relative centrifugal force for 10 to 15 minutes at 5°C, and the separated plasma was stored in labeled, screw-capped polypropylene tubes at temperatures ≤ −20°C within 1 hour of collection.

Plasma CP-609,754 concentrations were assayed at Pfizer Global Research and Development (Groton, CT) with a validated assay method. Plasma aliquots had internal standard added (Pfizer compound CP-595,730) and were acidified with 1% acetic acid. Drug and internal standard were extracted with a Waters OASIS MCX (10 mg) SPE 96-well extraction plate and were eluted with 5% ammonium hydroxide/95% methanol. The eluates were dried down and reconstituted in 50:50 acetonitrile:10 mmol/L ammonium acetate. Analytical separation was done with reverse phase liquid chromatography with a LUNA 5-μm C8(2) 2.00 × 50-mm column (Phenomenex, Torrance, CA) preceded by a 2.0-μm stainless steel precolumn filter. The detection method was turbospray tandem mass spectrometry done on a Sciex API 3000 mass spectrometer (PE Biosystems, Foster City CA). The lower limit of quantification for the assay was 1 ng/mL, and the upper limit of quantification was 250 ng/mL. The intra-assay accuracy and precision (as coefficient of variation) were, respectively, 94 and 4.4% at the lower limit of quantification, 93 and 2.3%, at the upper limit of quantification, and 93 to 110% and 2.3 to 5.5% over the quantifiable range.

Individual patient pharmacokinetic parameter values were estimated from each patient's concentration-time data with a noncompartmental approach. The parameters estimated were observed maximum plasma concentration (C_{max}), the time of occurrence of C_{max} (T_{max}), the observed end-of-dosing-interval plasma concentration (C_{min}), and the terminal phase half-life ($T_{1/2}$). For day 1 data, the area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\text{-inf}}$), and for day 15 data, the AUC over the dosing interval ($AUC_{0\text{-}\tau}$) and the accumulation ratio were calculated. C_{max}, T_{max}, and C_{min} were determined empirically. $T_{1/2}$ was calculated as ln(2) divided by the terminal phase rate constant, which was estimated with ordinary least-squares regression of time on log-transformed plasma concentration data from the terminal phase; visual examination of the aggregate plasma concentration data indicated that the terminal phase was present beginning 4 hours after dosing, so the 4-hour time point was used as the start of the terminal phase for all of the patients. AUC was calculated with the linear trapezoidal rule over the range of observed data; the extrapolated portion of $AUC_{0\text{-inf}}$ was calculated with the estimate of the terminal rate constant found in calculating $T_{1/2}$. The accumulation ratio was calculated as day 15 $AUC_{0\text{-}\tau}$ divided by day 1 $AUC_{0\text{-inf}}$.

Pharmacodynamics. The pharmacodynamic marker evaluated in this study was farnesyl transferase activity in peripheral blood mononuclear cells. Blood was collected into sodium citrate-containing mononuclear cell preparation tubes (Vacutainer CPT#362753, 8 mL; Becton Dickinson; Franklin Lakes, NJ) on day 1 and day 15 of cycle 1. For both once daily and twice daily dosing, the sampling schedule was predose and 2, 12, and 24 hours after the morning dose of CP-609,754.

Blood samples were stored upright at room temperature (18°C to 25°C) for no longer than 2 hours until processed at the study site for the collection of peripheral blood mononuclear cells. Peripheral blood mononuclear cell pellets were prepared at the study site with the following procedure: Vacutainer tubes were inverted 8 to 12 times to mix the anticoagulant with blood. The samples were centrifuged at 1500 to 1800 relative centrifugal force at room temperature in a horizontal (swing-out head) rotor for 30 minutes (with no brake). The upper half of the plasma layer was discarded without disturbing the cell layer containing the peripheral blood mononuclear cells. The peripheral blood mononuclear cell layer was collected and transferred to a conical polypropylene centrifuge tube. The pooled peripheral blood mononuclear cells were resuspended in an excess of room temperature sterile PBS and then centrifuged for 10 to 15 minutes at 300 relative centrifugal force. The supernatant was aspirated and discarded and the wash procedure repeated two more times (total of three PBS washes). The pellet was resuspended in room temperature sterile PBS and a cell count done with an aliquot from the resuspended pellet. The sample was then recentrifuged (15 minutes at 300 relative centrifugal force) and the supernatant completely removed. The cell pellets were immediately flash-frozen in liquid nitrogen and the sample stored at −80°C until shipped.

Peripheral blood mononuclear cell homogenates were assayed for farnesyltransferase activity at Pfizer Global Research and Development by measuring the transfer of the farnesyl group from [^{3}H]farnesyl PP_i (FPP) to a prenyl acceptor (bioti-

nylated-KTKCVIS peptide) with the Scintillation Proximity Assay (Amersham Life Science Products, Arlington Heights, IL).

Pharmacokinetic/Pharmacodynamic Analysis. Peripheral blood mononuclear cell farnesyltransferase activity (expressed as fraction of pretreatment activity) was modeled as being related directly to the plasma CP-609,754 concentration measured at the corresponding time with the E_{max} model of drug action,

peripheral blood mononuclear cell farnesyltransferase activity

$$= 1 - \frac{I_{max} \times C_p}{IC_{50} \times C_p}$$

where I_{max} is the maximum extent of inhibition of farnesyltransferase activity, IC_{50} is the Michaelis constant of the inhibition process, and C_p is the plasma concentration of CP-609,754 measured at the same time as the peripheral blood mononuclear cell farnesyltransferase activity. The model was applied to all of the 2-hour postdose CP-609,754 concentrations and peripheral blood mononuclear cell farnesyltransferase activity data simultaneously to derive population estimates of I_{max} and IC_{50}. The 2-hour postdose data were selected because they are the observed data closest to the time of maximal plasma concentration of CP-609,754 and, therefore, of maximal inhibition of peripheral blood mononuclear cell farnesyltransferase activity. Parameter estimation was done by nonlinear regression analysis (WinNonlin, Pharsight Corporation, Mountain View CA).

RESULTS

Demographics. A total of 21 patients were enrolled in the study. One patient with non–small-cell lung cancer withdrew from the study after developing a coagulopathy with an increased prothrombin time after 14 days of therapy at the 20 mg once daily dose. The patient was receiving warfarin for a history of deep venous thrombosis, so the possibility of drug interaction could not be excluded. Patient characteristics are as outlined in Table 2.

Dose Escalation. A total of 68 cycles was administered, and the median number of cycles per patient was 6.3 (range, <1 to 13). The mean duration of therapy for all patients treated was 89 days. Dose escalation proceeded per protocol guidelines until the 1280 mg once daily dose level was reached. As a result of the large number of tablets required for dose administration, the 1280 mg once daily dose level was abandoned, and the 640 mg twice daily dosing cohort was expanded to include three patients. Although no DLTs were reported during the first 14 days of treatment for each of the three patients enrolled at this dose level, additional accrual to a higher dose level was interrupted for 46 days due to the lack of available study drug. During this interval, a single patient within the 640 mg twice daily dosing cohort experienced grade 3 febrile neutropenia after two cycles of therapy (symptoms resolved within 7 days) and grade 3 peripheral neuropathy after three cycles of therapy. The peripheral neuropathy lasted >7 days and resulted in discontinuation of the study drug; however, this was not considered a DLT because the patient had completed more than one cycle of therapy. Although this patient was not considered to have a DLT per protocol specifications, this dose level was expanded to include a total of six patients. One additional patient developed grade 3 neuropathy consisting of dizziness and unsteady gait after 11 days of therapy. The drug was held for 5 days and then restarted after the neuropathy decreased to < grade 2. After taking the drug for an additional 3 days, the neuropathy returned, and the patient discontinued study protocol, which resulted in the only DLT reported during the study. No additional DLTs occurred; however, the study was halted at the 640 mg twice daily dose level due to lack of available study drug and concerns about patient compliance with the large number of tablets required for additional dose escalation.

Hematologic Toxicity. When considering both treatment- and nontreatment-related toxicities, lymphopenia and

Table 2 Patient characteristics

		No. of patients (N = 21)
Female/male		7/14
Age (y)		
Mean		61.1
Range		47–73
Eastern Cooperative Oncology group performance status		
0		8
1		12
2		1
Prior treatment		
Radiation		8
Chemotherapy		20
Surgery		21
Cancer diagnosis		
Urothelial and kidney		2
Colorectal		7
Lung cancer	Non–small-cell lung cancer = 3, small-cell lung cancer = 1	4
Sarcoma		4
Other	Pancreas = 1, gastric = 1, GIST = 1, thyroid = 1	4

Abbreviation: GIST, gastrointestinal stromal tumor.

Table 3 Treatment-related adverse events and DLT

Dose of CP-609,574	No. of patients	Grade 3 and 4 adverse events (no. of patients)	DLT (no. of patients)
20 mg QD	3	Grade 3 coagulation time increased (1), grade 3 constipation (1)	
10 mg BID	1	Grade 3 depersonalization (1)	
40 mg QD	1		
20 mg BID	1		
80 mg QD	1		
40 mg BID	1		
160 mg QD	1		
80 mg BID	1		
320 mg QD	1	Grade 3 dyspepsia (1), hypokalemia (1)	
160 mg BID	1		
640 mg QD	1	Grade 3 anemia (1)	
320 mg BID	1	Grade 3 hypokalemia (1)	
640 mg BID	6	Grade 3 asthenia (1), pain (1), febrile neutropenia (1), leukopenia (2), confusion (1), neuropathy (2)	Grade3neuropathy(1)

Abbreviations: QD, once daily; BID, twice daily dosing.

anemia were the most common hematologic toxicities encountered during the study. Grade 3 lymphopenia occurred throughout most of the dose levels studied. Anemia also occurred throughout the dose levels studied but was usually mild (grade 1 or 2). One patient treated at the 640 once daily dose level did, however, develop grade 3 anemia. Four patients developed leukopenia (one patient, grade 1; one patient, grade 2; and two patients, grade 3) within the 640 mg twice daily dosing cohort. One patient in the 640 mg twice daily dosing cohort developed grade 3 febrile neutropenia after 2 months of therapy. Although no source was identified, the fever resolved with broad spectrum antibiotics, and the patient restarted the study drug after resolution of symptoms. An additional cycle of therapy was administered without recurrence of neutropenia or fever. Thrombocytopenia was not seen in the lower dose levels, but two patients in the 640 mg twice daily dosing cohort developed grade 2 and 3 thrombocytopenia, respectively. All treatment-related grade 3 and grade 4 adverse events are outlined in Table 3.

Nonhematologic Toxicity. When considering both treatment-related and nontreatment-related toxicities, grade 1 to 2 elevations or reductions in serum electrolytes were seen at all dose levels studied. Grade 3 hypokalemia was reported in patients at the 20, 160, 320 mg once daily dose levels and at the 320 mg twice daily dose level (one patient at each dose level); the events at the 20 and 160 mg once daily dose levels were not attributed to study drug. Grade 3 hypocalcemia occurred in one patient at the 20 mg once daily dose level but was not considered to be due to study treatment. One patient in the 10 mg twice daily dose level developed grade 2 hyperbilirubinemia, and grade 4 elevations in alkaline phosphatase and gamma glutamyltransferase that were attributed to progression of disease. Two additional patients developed grade 3 elevations of gamma glutamyltransferase at the 80 mg once daily and 40 mg twice daily dose levels, respectively. Grade 4 hyponatremia and grade 3 elevation in serum creatinine also occurred in one patient with colorectal carcinoma treated at the 160 mg once daily dose level. Additional evaluation revealed that the patient had progression of disease within the pelvis causing ureteral obstruction.

The most frequent adverse events encountered at the 640 mg twice daily dose level are listed in Table 4. Grade 3 peripheral neuropathy occurred in one patient after three cycles of therapy, and the study drug was discontinued after the neuropathy did not resolve to grade 1 within 7 days. A second patient also developed grade 3 neuropathy after 11 days of therapy at the 640 mg twice daily dose level. Other grade 1 nonhematologic toxicities (not listed in Table 4) included (one each), myasthenia, pharyngitis, taste perversion, dyspepsia, abdominal pain, and fever.

Table 4 Common adverse events at the 640 mg twice daily dose level ($N = 6$)

	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy			2	
Asthenia			1	
Pain		1	1	
Diarrhea	1	1		
Nausea	2			
Proctitis		1		
Vomiting	1			
Bilirubinemia	1			
Increase creatinine	1			
Hypocalcemia	1			
Leg cramps		1		
Confusion			1	
Increased cough	2			
Photophobia		1		

Table 5 Patients noted to have stable disease > 2 months

Tumor type	Dose level	Duration of stable disease (days)
Bronchoalveolar carcinoma	20 mg QD	112
Renal cell carcinoma	20 mg BID	126
Colorectal carcinoma	80 mg QD	94
Bronchoalveolar carcinoma	80 mg BID	198
Colorectal carcinoma	320 mg BID	68
Renal cell carcinoma	640 mg BID	71
Colorectal carcinoma	640 mg BID	162
Hepatocellular carcinoma	640 mg BID	88
Thyroid carcinoma	640 mg BID	367
Colorectal carcinoma	640 mg BID	114

Abbreviations: QD, once daily; BID, twice daily.

Table 6 Pharmacokinetic parameters for patients receiving CP-609,754 in individual subject twice daily dosing cohorts

Day	Dose (mg)	Time	AUC (h·ng/mL)	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	$T_{1/2}$ (h)
1	10	a.m.	NC	7.9	1	NC	NC
		p.m.	NC	9.9	2	NC	NC
	20	a.m.	NC	18	1	NC	NC
		p.m.	49.6	8.9	2	NC	4
	40	a.m.	379	170	1	NC	2.4
		p.m.	422	140	1	NC	2.4
	80	a.m.	431	120	2	NC	3.5
		p.m.	288	46	3	NC	3.3
	160	a.m.	1510	480	2	NC	1.8
		p.m.	1560	240	4	NC	2.3
	320	a.m.	3560	1100	2	NC	2.7
		p.m.	3810	830	3	NC	1.8
2	10	a.m.	73.4	27	1	<LLOQ	NC
		p.m.	27.9	6.3	1	1.5	NC
	20	a.m.	59.1	17	1	<LLOQ	NC
		p.m.	59.6	11	2	2.0	NC
	40	a.m.	438	140	1	3.5	2.7
		p.m.	415	160	1	5.0	3.5
	80	a.m.	273	59	2	4.4	2.9
		p.m.	156	24	2	4.9	NC
	160	a.m.	1190	230	4	17	2.2
		p.m.	1040	130	2	22.0	3.8
	320	a.m.	2260	600	2	14	2.1
		p.m.	5190	920	4	35.0	1.7

NOTE. AUC equals $AUC_{0\text{-inf}}$ (AUC extrapolated to infinity) for day 1 and $AUC_{0\text{-}\tau}$ (AUC of dosing interval) for day 15.
Abbreviations: NC, not calculated; LLOQ, lower limit of quantitation.

Tumor Response. Patients were evaluated for response after the first two cycles and every two cycles thereafter. There were no objective responses observed, but 10 patients had prolonged stabilization of disease for >2 months (range, 68 to 367 days, see Table 5). The majority of patients with stable disease had colorectal cancer (four patients), bronchoalveolar carcinoma (two patients), or renal cell carcinoma (two patients). An additional patient with hepatocellular carcinoma had stable disease for 3 months before discontinuing the study drug secondary to neuropathy. The longest duration of stable disease (367 days) was observed in a patient with thyroid carcinoma who later discontinued the drug due to mild renal insufficiency. The renal insufficiency did not improve after discontinuation of the drug and was attributed to the patient's diabetes mellitus.

Pharmacokinetics. Pharmacokinetic data were obtained for eight patients receiving CP-609,754 by once daily dosing and for 11 patients receiving CP-609,754 by twice daily dosing. The pharmacokinetic parameter values for patients receiving CP-609,754 in individual subject twice daily dosing cohorts are listed in Table 6. The mean pharmacokinetic parameter values for patients in the 640 mg twice daily dosing cohort, the only twice daily cohort with multiple patients, are listed in Table 7, and the mean day 15 plasma CP-609,754 concentration-time curve for patients in this cohort is shown in Fig. 2. Within the 640 mg twice daily dosing cohort, the absorption of CP-609,754 is fairly rapid, with T_{max} between 1 and 2 hours after morning dosing and ~4 hours after evening dosing. The half-life is short, ~3 hours. The accumulation of CP-609,754 with multiple dosing is less than expected, with a mean accumulation ratio of 0.75 for the morning dose and 0.54 for the evening dose. C_{min} for the evening dose is close to the target concentration of 118 ng/mL.

Pharmacodynamics. Peripheral blood mononuclear cell farnesyltransferase activity data were obtained for three patients receiving CP-609,754 by once daily dosing and for nine patients receiving CP-609,754 by twice daily dosing. Plasma concentration data were obtained for all of these patients. Table 8 lists the

Table 7 Mean (SD) of pharmacokinetic parameters for patients receiving CP-609,754 in 640 mg twice daily dosing cohort

Day and time	Number	AUC (h·ng/mL)	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	$T_{1/2}$ (h)
Day 1	6					
a.m.		4640 (2670)	1250 (660)	1.8 (0.4)	NC	2.4 (0.3)
p.m.		6470 (4180)	947 (691)	4.5 (1.2)	NC	3.0 (0.7)
Day 15	5					
a.m.		3650 (1190)	1110 (330)	1.0 (0.0)	46.0 (21.0)	3.2 (0.2)
p.m.		3480 (1410)	656 (311)	3.8 (1.3)	101 (54)	2.9 (1.0)

NOTE. AUC equals $AUC_{0\text{-inf}}$ (AUC extrapolated to infinity) for day 1 and $AUC_{0\text{-}\tau}$ (AUC of dosing interval) for day 15.
Abbreviations: NC, not calculated.

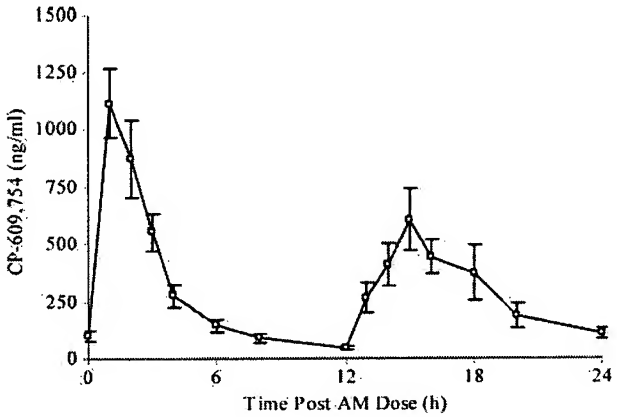

Fig. 2 Mean (±SE) day 15 plasma CP-609,754 concentration-time curve for patients receiving 640 mg CP-609,754 twice daily (n = 5).

day 1 and day 15 2-hour postmorning dose CP-609,754 concentrations and peripheral blood mononuclear cell farnesyltransferase activity values according to dose. The 2-hour postdose peripheral blood mononuclear cell farnesyltransferase activity represents the lowest measured peripheral blood mononuclear cell farnesyltransferase activity for most patients. Greater than 70% inhibition of peripheral blood mononuclear cell farnesyltransferase activity was achieved at that time point by all patients receiving ≥160 mg CP-609,754 once daily or twice daily dosing. The 2-hour postdose peripheral blood mononuclear cell farnesyltransferase activity is inversely correlated with the daily dose ($r = -0.81$). Table 9 lists the day 15 morning and evening predose CP-609,754 concentrations and peripheral blood mononuclear cell farnesyltransferase activity values. For twice daily dosing, the morning predose peripheral blood mononuclear cell farnesyltransferase activities are mostly lower than the evening predose activities. This is so because the end of dosing interval concentrations after the evening dose are, for the most part, higher than for the morning dose, likely due to a food effect from the evening meal (see Fig. 2). For the patients dosed at 640 mg twice daily dosing, the peripheral blood mononuclear cell farnesyltransferase activity is, on average, 60% inhibited at the evening predose time point, which is the time of nadir plasma concentration for twice daily dosing of CP-609,754.

The E_{max} model yielded a good fit of the combined day 1 and day 15 2-hour postmorning dose data, as shown in Fig. 3 (r^2, 0.51). The population estimate of I_{max} is 0.92 (SE, 0.03) and of IC_{50} is 31.6 (SE, 8.5) ng/mL. The relationship between the 2-hour postdose peripheral blood mononuclear cell farnesyltransferase activity and twice daily dose was calculated with plasma CP-609,754 concentrations predicted from a linear relationship between morning twice daily dose and 2-hour postdose concentration. Using this relationship, a 200 (95% confidence interval, 5–375) mg twice daily dose is predicted to provide, on average, 90% maximal inhibition of peripheral blood mononuclear cell farnesyltransferase activity, and a dose of 400 (95% confidence interval, 225–580) mg is predicted to result in, on average, 95% maximal inhibition.

There is no predictive relationship between the degree of inhibition of farnesyltransferase and the clinical response of the patients (stable disease *versus* progressive disease) in the small number of patients in whom farnesyltransferase data were available.

DISCUSSION

In the phase I setting, where patients have advanced refractory disease and most are enrolled at dose levels below those thought to be maximally efficacious, it is only infrequently possible to show a biological effect of therapy by monitoring tumor response. In contrast, cellular effects can often be showed convincingly, even in the phase I setting, with pharmacodynamic measures. Such a demonstration increases the confidence-in-mechanism for the investigational agent, thereby providing impetus for its continued development. Pharmacodynamic monitoring was undertaken in this study to show the desired cellular effect of treatment with CP-609,754 and the inhibition of its molecular target, farnesyl transferase. Farnesyltransferase activity was measured in peripheral blood mononu-

Table 8 Day 1 and day 15 2-hour postmorning dose plasma CP-606,754 concentrations (C2 h) and fractional FTase activity values

		Day 1		Day 15	
Schedule	Dose (mg)	C2 h (ng/mL)	FTase activity (fraction)	C2 h (ng/mL)	FTase activity (fraction)
Once daily	160	270	0.264	190	NO
	320	670	0.157	1300	0.208
	640	1100	0.034	810	0.036
Twice daily	40	98	0.379	140	0.344
	80	120	0.421	59	0.299
	160	480	0.076	85	0.150
	320	1100	0.093	600	0.133
	640	970	0.077	NO	NO
	640	1300	0.121	940	0.173
	640	1600	0.050	1000	0.059
	640	1000	0.085	990	0.071
	640	249	0.285	225	0.140

NOTE. Each row represents an individual patient.
Abbreviations: FTase, farnesyltransferase; NO, not obtained.

Table 9 Day 15 morning and evening predose plasma CP-606,754 concentrations (C0 h) and fractional FTase activity values

		Morning		Evening	
Schedule	Dose (mg)	C0 h (ng/mL)	FTase activity (fraction)	C0 h (ng/mL)	FTase activity (fraction)
Once daily	160	3	0.221		
	320	6	0.431		
	640	8	0.207		
Twice daily	40	11	0.897	3.5	0.904
	80	15	0.335	4.4	0.373
	160	24	0.244	17	0.212
	320	21	0.484	14	0.317
	640	120	0.409	27	0.933
	640	160	0.118	65	0.155
	640	86	NO	NO	NO
	640	33	0.269	30	0.280
	640	78	0.123	37	0.225

NOTE. Each row represents an individual patient.
Abbreviations: FTase, farnesyltransferase; NO, not obtained.

clear cell cells because of the ease of obtaining serial specimens. The data, although constituting a small data set, show that a clinically significant degree of inhibition of farnesyltransferase activity was likely achieved with the higher doses of CP-609,754 evaluated in this study.

On the basis of mouse tumor experiments, it is predicted that CP-609,754 will be clinically efficacious against ras-expressing tumors if concentrations are maintained above 118 ng/mL. C_{min} values after the evening dose of 640 mg twice daily approached this target value (Table 7). After the morning dose, concentrations of CP-609,754 fell below the target value after ~8 hours (Fig. 2). This indicates that a dose of 640 mg twice daily is close to but slightly less than the dose needed to achieve the preclinical target concentration values.

The toxicity profile for 640 mg twice daily dosing, the highest dose evaluated in this study, was favorable, although two patients developed significant neurotoxicity, which resulted in discontinuation of study drug. One patient developed peripheral neuropathy after 3 months of therapy; however, this patient was not considered a DLT because more than one cycle of therapy was administered before developing neuropathy that resulted in study drug discontinuation. Although the event was not considered a DLT, this dose cohort was expanded to six patients to additionally assess delayed toxicity at the 640 mg twice daily dose level. A second patient developed dizziness and unsteady gait after 11 days of therapy. The second patient's symptoms resolved with discontinuation of CP-609,754 but recurred shortly after the drug was restarted, resulting in the study's only reported DLT. Although the etiology of the neuropathy is unknown, similar reports of neurotoxicity have been seen in phase I testing of other drugs designed to inhibit farnesyltransferase (12, 13).

Elevations in creatinine have also been seen in patients treated with other farnesyltransferase inhibitors in phase I or II clinical trials (14–16). Two patients treated on this study developed elevations in serum creatinine; however, neither was considered to be secondary to drug therapy. One patient with an elevated creatinine developed progression of disease, resulting in urinary obstruction, and the second patient developed mild renal insufficiency after completing 13 cycles of therapy. The renal insufficiency did not resolve with discontinuation of study drug and was attributed to an underlying diagnosis of diabetic nephropathy. Although gastrointestinal side effects have been dose limiting for other farnesyltransferase inhibitors in clinical development (16, 17), only mild to moderate gastrointestinal side effects were reported with CP-609,754. All patients responded to supportive care and these events were not dose limiting.

Hematologic toxicity was mild in the lower dose levels with anemia being the most common laboratory abnormality noted. One patient developed febrile neutropenia at the 640 mg twice daily dose level during the second cycle of therapy. After treatment with antibiotics and study drug discontinuation for 5 days, the neutropenic fever resolved, and the patient restarted CP-609,754 without dose reduction. The patient received ~30 additional days of therapy without recurrence of neutropenia or fever. However, the study drug was discontinued after three

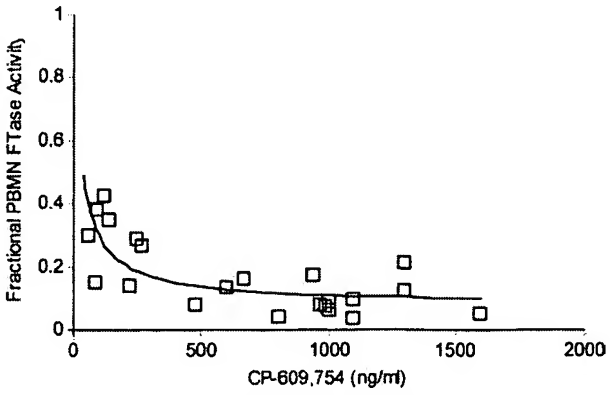

Fig. 3 The E_{max} pharmacokinetic/pharmacodynamic model fit of the combined day 1 and day 15 2-hour postmorning dose fractional peripheral blood mononuclear cell (PBMN) Farnesyltransferase (FTase) activity data. The observed data are shown as symbols, whereas the model fit of the data are shown as a solid line.

cycles when the patient developed grade 3 peripheral neuropathy that did not resolve with discontinuation of study drug. Mild to moderate leukopenia and lymphopenia were also seen. This is not unexpected because Ras plays an important role in the activation of T cells and natural killer cells (18), and lymphopenia has been seen as a side effect during preclinical, as well as phase I development of other farnesyltransferase inhibitors (12, 19). The significance of this finding is also difficult to determine in patients who have received extensive therapy for metastatic cancer; however, the absence of opportunistic infections is clinically reassuring. One patient with non–small-cell lung cancer developed coagulopathy with an increased prothrombin time after receiving 14 days of therapy at the 20 mg once daily dose and was withdrawn from study. The patient was receiving warfarin for a history of deep venous thrombosis, so the possibility of drug interaction could not be excluded. Grade 3 hypokalemia was also frequently seen on weekly lab evaluation. The etiology of the hypokalemia is unknown and has not been reported for other farnesyltransferase inhibitors in clinical development.

Although no measurable responses occurred during the study, 10 patients had prolonged stabilization of disease > 2 months (see Table 5). Patients with stable disease had variety of tumor types, including colorectal, bronchoalveolar, renal cell, hepatocellular, and thyroid carcinoma. All patients treated at the 640 mg twice daily dose had stable disease for >2 months, except for one patient who developed neurotoxicity and stopped therapy after 11 days of treatment. The longest duration of stable disease (367 days) was observed in the patient with thyroid carcinoma treated at the 640 mg twice daily dose level. The mean duration of response for patients who tolerated therapy in this cohort was 160 days (range, 71 to 367 days), which shows that chronic oral dosing of CP-609,754 is feasible and could possibly result in prolonged disease stabilization.

In conclusion, this study has showed that chronic oral dosing with CP-609,754 can inhibit farnesylation in peripheral blood mononuclear cell cells at doses that were easily tolerable. The maximum-tolerated dose was not reached in this study due to the large number of tablets that would have been required for additional dose escalation. On the basis of the safety findings and the pharmacokinetic and pharmacodynamic analyses, the recommended dose for phase II testing is ≥640 mg twice daily. Treatment with CP-609,754 resulted in stabilization of disease for >2 months in all of the patients who could tolerate the 640 mg twice daily dose; therefore, future study should be considered.

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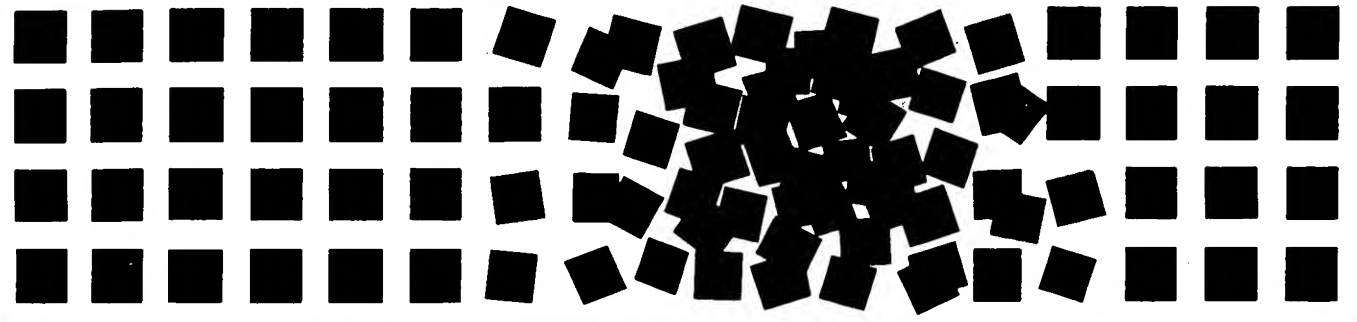

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CHAPTER 22

Cancer of the Head and Neck

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SECTION 1

Tumors of the Nasal Cavity and Paranasal Sinuses, Nasopharynx, Oral Cavity, and Oropharynx

Cancers of the upper aerodigestive tract represent a diverse number of diseases. Each bears its own unique set of epidemiologic, anatomic, pathologic, and treatment considerations. This section reviews such considerations based on four anatomically defined regions: the nasal cavity and paranasal sinuses, the nasopharynx, the oral cavity, and the oropharynx.

There are general principles regarding these cancers that may be considered. Such principles involve anatomy (*i.e.*, anatomy primarily of the regional lymph nodes within the head and neck), pathology, staging and screening, and general principles of treatment involving single-modality or multimodality therapy, which are relevant to all sites.

ANATOMY

An understanding of the regional lymph node anatomy is critical to the care of head and neck cancer patients. There are several major lymphatic chains in the neck containing nearly 200 lymph nodes that run parallel to the jugular veins, spinal accessory nerve, and facial artery and into the submandibular triangle (Fig. 22–1). To facilitate communication regarding cervical lymph node anatomy, the regions of the neck have been characterized by levels (Fig. 22–2).[1,2]

Level I includes nodes within the submental triangle and the submandibular triangle. The submental triangle extends from the midline anteriorly to the anterior belly of the digastric muscle posteriorly. Its third border is formed by the hyoid bone inferiorly. The submandibular triangle is bounded by the mandible superiorly. The anterior and the posterior belly of the digastric muscle complete the triangle.

Level II includes the jugular nodes extending from the subdigastric area down to the carotid bifurcation and the nodes surrounding the spinal accessory nerve from the jugular foramen to the posterior border of the sternocleidomastoid muscle. It includes the lymph nodes in the upper posterior cervical triangle above the entrance of the spinal accessory nerve into this triangle.

Level III represents the nodal area principally along the jugular vein between the carotid and its bifurcation, the posterior border of the sternocleidomastoid muscle, and the omohyoid muscle.

Level IV constitutes nodal areas below the omohyoid muscle above the level of the clavicle and between the carotid vessels anteriorly and the omohyoid muscle posteriorly.

Level V represents nodes in the posterior cervical triangle. Its borders are formed by the posterior edge of the sternocleidomastoid muscle, the level of the entrance of the spinal accessory nerve, the trapezius muscle, and the posterior belly of the omohyoid muscle.

Specific sites within the aerodigestive tract have a predetermined drainage pattern. A knowledge of this pattern aids in diagnosis and impacts on therapy. Drainage patterns are addressed in each of the anatomic subsites detailed in this chapter.

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SECTION 2

Tumors of the Larynx and Hypopharynx

LARYNX

Considering that cancer occurs in the larynx 13 times less frequently than in the lung, 10 times less frequently than in the breast, and 9 times less frequently than in the prostate gland, the number of publications that have appeared in the North American literature on laryngeal cancer during the previous 5 years seems excessive. This considerable body of writing probably reflects the perceived importance of this disease relative to its potential impact on people's communicative and functional skills in society. A new attitude seems to exist among oncologists that is characterized by a keener concern for quality of life and death, and this applies especially to laryngeal cancer, for which any threat to a patient's "voice box" is associated with profound psychological overtones. Curing the cancer at any cost is no longer accepted casually, and now more than ever before, a premium is placed on return to a productive and useful lifestyle after cancer treatment. Nowhere in the oncology community is this change more vividly demonstrated than in the treatment of larynx cancer. Therefore, investigations continue into the methods of conservation laryngeal surgery, different radiation therapy strategies, and recently, combined chemotherapy and radiation therapy protocols designed for larynx preservation.[1-3] Although the cure rates of the various laryngeal malignancies have not changed dramatically during recent years,[4] the treatment options and the sequencing of those options have, and a higher percentage of laryngeal cancer patients are retaining their larynx in the process.

EPIDEMIOLOGY AND ETIOLOGY

Even though considerable differences between countries exist in the incidence of larynx cancer, its distribution within each country is consistent. For example, the disease most commonly affects middle-aged or older men who have smoked tobacco[5,6] and have drunk alcohol.[7,8] Laryngeal cancer rarely occurs in people who have done neither. In the United States during 1990, more than 12,000 new larynx cancers were diagnosed, and about 10,000 of those were in men. Even though this disease has always been more common in men, the current 4.5:1 ratio of men to women seems to be changing as the smoking habits of the sexes change—in 1956, this ratio was 15:1.[7] The peak incidence of larynx cancer is in the sixth decade. The disease occurs in young people only rarely.[8]

The following etiologic factors have been implicated in laryngeal cancer: voice abuse and chronic laryngitis[9,10]; certain dietary factors[11-13]; chronic gastric reflux[14]; and exposure to wood dust,[15] nitrogen mustard, asbestos, and ionizing radiation.[15-18] Most consistently seen, however, is the association between larynx cancer and smoking, whether by pipe, cigarette, or cigar.[15] There seems to be an association with heavy alcohol intake and larynx cancer, and an enhancement of the already present risk factors associated with smoking.[19] On the other hand, some studies have failed to demonstrate an interdependent causal effect for alcohol intake and larynx cancer.[20] The issue of alcohol, smoke, and carcinogenesis is complicated by the nutritional deficiencies that usually occur in alcoholics.[13] In the larynx, this complex issue is more specifically defined by the fact that whatever the role of alcohol, it is apparently more significant in supraglottic than in glottic cancers.[21-24] As the current generation of those youngsters using smokeless tobacco matures, there may be some alteration of the relative incidence of supraglottic and glottic cancers. Those worldwide data that show large variations of laryngeal cancer statistics consistently reflect the smoking and drinking habits of the individual countries.[25] Also, the sites within the larynx affected by cancers vary considerably between countries. This distribution is shown in Table 22–29,[9,24,26-28] which represents a compendium of worldwide data that addresses the relative distributions of cancer within the larynx.

SURGICAL AND DEVELOPMENTAL ANATOMY

The larynx is a uniquely complicated organ that is strategically located so that significant alteration of its anatomy by either surgery or cancer can have a noticeable impact on digestive and respiratory physiology. The organ consists of three subsites, which are the glottis (paired true vocal cords), the supraglottis, and the subglottis. Because of different embryologic development and different lymphatic patterns that are subsite specific, discussing larynx cancers without specific reference to the exact location(s) within that structure invites inaccuracies in staging and miscalculations in treatment planning.

The larynx consists of five cartilages: the cricoid, the epiglottis, the paired arytenoids, and the shield-like thyroid cartilage. Suspended within the endolarynx are the mobile true vocal cords, which are collectively known as the *glottis*. That portion above the glottis, the supraglottis, consists of the false vocal cords, the epiglottis, and the aryepiglottic folds. These folds form the junction with the hypopharynx. The medial wall of the aryepiglottic fold is within the endolarynx, and its

TABLE 22–29. Geographic Variations in Larynx Cancer Sites*

Country	No. of Patients n	Site		
		Supraglottic (%)	Glottic (%)	Subglottic (%)
Japan[9]	6360	49	50	0.9
Finland[24]	638	67	32	1
Yugoslavia[26]	722	62	35	3.5
USA[27]	1645	34	65	1
Sweden[28]	578	11	87	2

* Relative incidence of larynx cancer by anatomic site and country. Notice variation between supraglottic and glottic incidence relative to different countries, but the relative consistency of subglottic occurrence.

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SECTION **3**

Tumors of the Salivary Glands and Paragangliomas

The same group of neoplasms affect all salivary gland tissue, but with a predictable difference in type for the different anatomic sites. The major salivary glands consist of paired parotids in the preauricular area, paired submandibulars under the mandible, and paired sublinguals in the floor of the mouth. The minor salivary glands, on the other hand, are ubiquitious in the upper aerodigestive tract, occurring especially throughout the oral and nasal cavities and the paranasal sinuses. The likelihood of a neoplasm being malignant is highest in the sublingual and minor salivary glands, least in the parotids, and intermediate in the submandibular glands. Overall, salivary gland cancers make up about 3% of all head and neck malignancies diagnosed in North America each year, most of which are in the parotid gland. Overall, sublingual and minor salivary gland cancers are unusual.[1]

ANATOMY

The parotid gland is tightly compacted in the area immediately anterior and inferior to the external ear. It is best thought of in a three-dimensional sense, with the deep portion extending medially around the posterior rim of the ascending ramus of the mandible into the parapharyngeal space. The superficial part of the gland lies on the masseter muscle and extends

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CHAPTER **38**

Gynecologic Tumors

Gynecologic cancer represents 12.7% of all cancers that occur in women and accounts for 9.8% of all cancer deaths.[1] Table 38–1 lists the estimated number of new cases and deaths from gynecologic malignancies in 1992.

The physician who diagnoses and treats patients with cancer of the female genital tract must have a thorough understanding of the pathophysiology of the disease and the various therapeutic options that are available. In this chapter, we provide current information on all the female genital cancers except ovarian cancer, which is discussed separately in Chapter 39. We describe the epidemiology, natural history, routes of spread, and pathologic characteristics that affect treatment planning. We emphasize methods of diagnosis and current therapeutic options.

CARCINOMA OF THE VULVA

Carcinoma of the vulva accounts for 3% to 4% of all female genital cancers, and squamous cell cancer accounts for 90% of vulvar cancers. Other cell types that can be found in the vulva include malignant melanoma, basal cell carcinoma, and adenocarcinoma of the Bartholin's and Skene's glands. Primary vulvar sarcoma and verrucous carcinoma occur infrequently. Paget's disease can be associated with invasive adenocarcinoma of the sweat glands.

Vulvar cancers tend to develop slowly. They spread by direct continuity to adjacent tissues or by the lymphatics to the inguinal lymph nodes. Treatment is usually surgical, which in the past resulted in physical disfigurement and sexual dysfunction.[2] However, clinical studies of this disease report alternative methods of therapy that modify treatment to reduce disfigurement while improving survival.

EPIDEMIOLOGY

Carcinoma of the vulva accounts for 3% to 4% of all primary genital cancers in women. The median age for patients with carcinoma in situ of the vulva is 44.[3–7] For those with microinvasive carcinoma, the median age is 58.[7,8] Patients with frankly invasive carcinoma have a median age of 61.[9,10] Some researchers suggest that carcinoma in situ and microinvasive carcinoma are being seen more frequently and are occurring in younger women, but that impression remains to be verified by large studies. The age-incidence associations for invasive cancer do not appear to have changed.

Japaze and colleagues reported no increase in the incidence of vulvar cancer in any ethnic group.[5] However, Mack and Casagrande reported that women of the lowest socioeconomic class had three times the incidence that was seen in women of the highest socioeconomic class.[11]

Medical illnesses associated with vulvar cancer are hypertension, cardiovascular disease, obesity, and diabetes.[8,12,13] A variety of sexually transmitted diseases, including granulomatous venereal disease, syphilis, herpes hominis type II, and condylomata acuminata, have been associated with vulvar carcinoma.[7,14] Recent evidence suggests an association between the human papillomavirus or the herpes simplex virus and vulvar neoplasia.[15–19] Other associations, such as leukoplakia of the vulva, genitourinary cancer, and an occupational history in the laundry and cleaning industries, were observed.[20] Patients with vulvar cancer have an increased incidence of anogenital carcinomas, especially cervical cancer.[21,22]

NATURAL HISTORY AND PATTERNS OF SPREAD

The association of carcinoma in situ, microinvasive carcinoma, and invasive vulvar carcinoma indicates a continuum

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CHAPTER **39**

Cancer of the Ovary

Ovarian cancer is the fourth most common cause of cancer death in women and the leading cause of gynecologic cancer death in the United States. More women die from ovarian cancer each year than from cervical and endometrial carcinoma combined. Incidence and mortality estimates for 1992 indicate that 21,000 new patients are diagnosed yearly, and 13,000 women die from this disease.[1] A steady increase in the age-adjusted cancer death rates in the United States has occurred during the past 25 years, and similar increases have occurred in other industrialized nations.[2] Approximately 1 in every 70 women will develop ovarian cancer, and approximately 1% of all female deaths result from this disease.

EPIDEMIOLOGY

The highest ovarian cancer rates are reported in highly industrialized countries. The notable exception is Japan, where rates of death from ovarian cancer are among the lowest in the world. Studies of migrant populations strongly suggest environmental influences. Japanese migrants to Hawaii and their first-generation offspring in the United States have a significantly higher incidence of ovarian cancer than Japanese women in Japan, but the incidence is still lower than that observed in the indigenous white population of the United States.[3,4]

In the United States, the common epithelial neoplasms usually develop in adult white populations. They rarely occur before menarche, but the rate of occurrence tends to increase significantly thereafter. Incidences range from 15.7 of 100,000 women in the 40 to 44 age group to 54 of 100,000 women in the 75 to 79 age group. In contrast, germ cell ovarian tumors are primarily seen in children and young women, and they occur frequently in nonwhite populations.

Several epidemiologic studies suggest that disordered endocrine function may contribute to the development of ovarian cancer. A higher incidence of epithelial tumors is seen in women with a lower mean number of pregnancies, in nulliparous women, and in women with a history of infertility.[5–7] Compared with a relative risk of 1.0 for nulliparous women, women who have had one to two pregnancies have a risk of 0.49 to 0.97, and women with three or more pregnancies have a relative risk of 0.35 to 0.76.[8] Each additional pregnancy appears to lower the risk by about 10%. No clear association between ovarian cancer and the administration of synthetic estrogens has been established, but oral contraceptives reduce ovarian cancer risk.[9–13] In a World Health Organization study, 368 women with ovarian cancer were compared with 2397 matched controls. The relative risk for women who had used oral contraceptives was 0.75.[13] Oral contraceptives are estimated to have prevented over 1700 cases of ovarian cancer in the United States.[12] Risk appears to fall after several months of contraceptive use, but the reduction is greatest for long-term users.

An increased frequency of ovarian thecomas has been described in patients who undergo long-term anticonvulsant therapy. This increase is probably related to variations in the patients' ability to metabolize anticonvulsant drugs.[14]

No association with a viral infection has been identified, but a lower than expected frequency of mumps and other viral exanthems has been reported for women with ovarian cancer.[15]

Cancers of the ovary and breast appear to share some common etiologic factors. For example, women with breast cancer have twice the expected risk for ovarian carcinoma. Women with ovarian cancer have a threefold to fourfold increase in the incidence of subsequent breast cancer. Most studies that have evaluated breast feeding have not found it to be a risk factor.